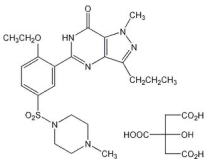
VIAGRA - sildenafil citrate tablet, film coated
Pfizer Laboratories Div Pfizer Inc

DESCRIPTION

VIAGRA®, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).
Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7.
VIAGRA (sildenafil citrate) is formulated as blue, film-coated rounded-diamond-shaped tablets equivalent to 25 mg, 50 mg and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.
Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina which is involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see **Pharmacodynamics**).
In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, an inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*.

Pharmacokinetics and Metabolism

VIAGRA is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25–63%). Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**). Both sildenafil and the metabolite have terminal half lives of about 4 hours.
Mean sildenafil plasma concentrations measured after the administration of a single oral dose of 100 mg to healthy male volunteers is depicted below:

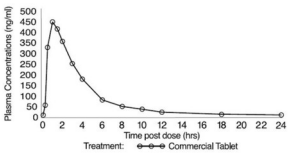


Figure 1: Mean Sildenafil Plasma Concentrations in Healthy Male Volunteers.

Absorption and Distribution
VIAGRA is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When VIAGRA is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Pharmacokinetics in Special Populations

Geriatrics
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma AUC values of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18–45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

Renal Insufficiency
In volunteers with mild (CLcr=50–80 mL/min) and moderate (CLcr=30–49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of VIAGRA (50 mg) were not altered. In volunteers with severe (CLcr=<30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

In addition, N-desmethyl metabolite AUC and Cmax values significantly increased 200% and 79% respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic Insufficiency
In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child Pugh class C) have not been studied.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Effects of VIAGRA on Erectile Response
In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections (RigiScan®), after VIAGRA administration compared with placebo. Most studies assessed the efficacy of VIAGRA approximately 60 minutes post dose. The erectile response, as assessed by RigiScan®, generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of VIAGRA on Blood Pressure
Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in sitting blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.3/5.3 mmHg). The decrease in sitting blood pressure was most notable approximately 1–2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with

25 mg, 50 mg and 100 mg of VIAGRA, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

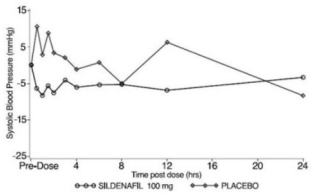


Figure 2: Mean Change from Baseline in Sitting Systolic Blood Pressure, Healthy Volunteers.

Effects of VIAGRA on Cardiac Parameters
Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of VIAGRA on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

TABLE 1. HEMODYNAMIC DATA IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE AFTER IV ADMINISTRATION OF 40 MG SILDENAFIL

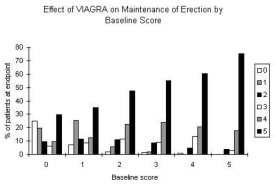
Means ± SD	**At rest**				**After 4 minutes of exercise**			
	n	**Baseline (B2)**	**n**	**Sildenafil (D1)**	**n**	**Baseline**	**n**	**Sildenafil**
PAOP (mmHg)	8	8.1 ± 5.1	8	6.5 ± 4.3	8	36.0 ± 13.7	8	27.8 ± 15.3
Mean PAP (mmHg)	8	16.7 ± 4	8	12.1 ± 3.9	8	39.4 ± 12.9	8	31.7 ± 13.2
Mean RAP (mmHg)	7	5.7 ± 3.7	8	4.1 ± 3.7	-	-	-	-
Systolic SAP (mmHg)	8	150.4 ± 12.4	8	140.6 ± 16.5	8	199.5 ± 37.4	8	187.8 ± 30.0
Diastolic SAP (mmHg)	8	73.6 ± 7.8	8	65.9 ± 10	8	84.6 ± 9.7	8	79.5 ± 9.4
Cardiac output (L/min)	8	5.6 ± 0.9	8	5.2 ± 1.1	8	11.5 ± 2.4	8	10.2 ± 3.5
Heart rate (bpm)	8	67 ± 11.1	8	66.9 ± 12	8	101.9 ± 11.6	8	99.0 ± 20.4

In a double-blind study, 144 patients with erectile dysfunction and chronic stable angina limited by exercise, not receiving chronic oral nitrates, were randomized to a single dose of placebo or VIAGRA 100 mg 1 hour prior to exercise testing. The primary endpoint was time to limiting angina in the evaluable cohort. The mean times (adjusted for baseline) to onset of limiting angina were 423.6 and 403.7 seconds for sildenafil (N=70) and placebo, respectively. These results demonstrated that the effect of VIAGRA on the primary endpoint was statistically non-inferior to placebo.

Effects of VIAGRA on Vision
At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, intraocular pressure, or pupillometry.

Clinical Studies
In clinical studies, VIAGRA was assessed for its effect on the ability of men with erectile dysfunction (ED) to engage in sexual activity and in many cases specifically on the ability to achieve and maintain an erection sufficient for satisfactory sexual activity. VIAGRA was evaluated primarily at doses of 25 mg, 50 mg and 100 mg in 21 randomized, double-blind, placebo-controlled trials of up to 6 months in duration, using a variety of study designs (fixed dose, titration, parallel, crossover). VIAGRA was administered to more than 3,000 patients aged 19 to 87 years, with ED of various etiologies (organic, psychogenic, mixed) with a mean duration of 5

years. VIAGRA demonstrated statistically significant improvement compared to placebo in all 21 studies. The studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with placebo.
The effectiveness of VIAGRA was evaluated in most studies using several assessment instruments. The primary measure in the principal studies was a sexual function questionnaire (the International Index of Erectile Function - IIEF) administered during a 4-week treatment-free run-in period, at baseline, at follow-up visits, and at the end of double-blind, placebo-controlled, at-home treatment. Two of the questions from the IIEF served as primary study endpoints; categorical responses were elicited to questions about (1) the ability to achieve erections sufficient for sexual intercourse and (2) the maintenance of erections after penetration.
The patient addressed both questions at the final visit for the last 4 weeks of the study. The possible categorical responses to these questions were (0) no attempted intercourse, (1) never or almost never, (2) a few times, (3) sometimes, (4) most times, and (5) almost always or always. Also collected as part of the IIEF was information about other aspects of sexual function, including information on erectile function, orgasm, desire, satisfaction with intercourse, and overall sexual satisfaction. Sexual function data were also recorded by patients in a daily diary. In addition, patients were asked a global efficacy question and an optional partner questionnaire was administered.
The effect on one of the major end points, maintenance of erections after penetration, is shown in Figure 3, for the pooled results of 5 fixed-dose, dose-response studies of greater than one month duration, showing response according to baseline function. Results with all doses have been pooled, but scores showed greater improvement at the 50 and 100 mg doses than at 25 mg. The pattern of responses was similar for the other principal question, the ability to achieve an erection sufficient for intercourse. The titration studies, in which most patients received 100 mg, showed similar results. Figure 3 shows that regardless of the baseline levels of function, subsequent function in patients treated with VIAGRA was better than that seen in patients treated with placebo. At the same time, on-treatment function was better in treated patients who were less impaired at baseline.



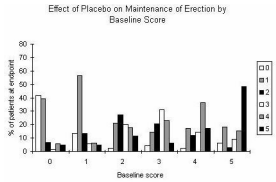


Figure 3. Effect of VIAGRA and Placebo on Maintenance of Erection by Baseline Score.

The frequency of patients reporting improvement of erections in response to a global question in four of the randomized, double-blind, parallel, placebo-controlled fixed dose studies (1797 patients) of 12 to 24 weeks duration is shown in Figure 4. These patients had erectile dysfunction at baseline that was characterized by median categorical scores of 2 (a few times) on principal IIEF questions. Erectile dysfunction was attributed to organic (58%; generally not characterized, but including diabetes and excluding spinal cord injury), psychogenic (17%), or mixed (24%) etiologies. Sixty-three percent, 74%, and 82% of the patients on 25 mg, 50 mg and 100 mg of VIAGRA, respectively, reported an improvement in their erections, compared to 24% on placebo. In the titration studies (n=644) (with most patients eventually receiving 100 mg), results were similar.

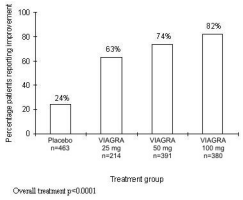


Figure 4. Percentage of Patients Reporting an Improvement in Erections.

The patients in studies had varying degrees of ED. One-third to one-half of the subjects in these studies reported successful intercourse at least once during a 4-week, treatment-free run-in period.
In many of the studies, of both fixed dose and titration designs, daily diaries were kept by patients. In these studies, involving about 1600 patients, analyses of patient diaries showed no effect of VIAGRA on rates of attempted intercourse (about 2 per week), but there was clear treatment-related improvement in sexual function: per patient weekly success rates averaged 1.3 on 50–100 mg of VIAGRA

vs 0.4 on placebo; similarly, group mean success rates (total successes divided by total attempts) were about 66% on VIAGRA vs about 20% on placebo.
During 3 to 6 months of double-blind treatment or longer-term (1 year), open-label studies, few patients withdrew from active treatment for any reason, including lack of effectiveness. At the end of the long-term study, 88% of patients reported that VIAGRA improved their erections.
Men with untreated ED had relatively low baseline scores for all aspects of sexual function measured (again using a 5-point scale) in the IIEF. VIAGRA improved these aspects of sexual function: frequency, firmness and maintenance of erections; frequency of orgasm; frequency and level of desire; frequency, satisfaction and enjoyment of intercourse; and overall relationship satisfaction.
One randomized, double-blind, flexible-dose, placebo-controlled study included only patients with erectile dysfunction attributed to complications of diabetes mellitus (n=268). As in the other titration studies, patients were started on 50 mg and allowed to adjust the dose up to 100 mg or down to 25 mg of VIAGRA; all patients, however, were receiving 50 mg or 100 mg at the end of the study. There were highly statistically significant improvements on the two principal IIEF questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) on VIAGRA compared to placebo. On a global improvement question, 57% of VIAGRA patients reported improved erections versus 10% on placebo. Diary data indicated that on VIAGRA, 48% of intercourse attempts were successful versus 12% on placebo.
One randomized, double-blind, placebo-controlled, crossover, flexible-dose (up to 100 mg) study of patients with erectile dysfunction resulting from spinal cord injury (n=178) was conducted. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA. On a global improvement question, 83% of patients reported improved erections on VIAGRA versus 12% on placebo. Diary data indicated that on VIAGRA, 59% of attempts at sexual intercourse were successful compared to 13% on placebo.
Across all trials, VIAGRA improved the erections of 43% of radical prostatectomy patients compared to 15% on placebo.
Subgroup analyses of responses to a global improvement question in patients with psychogenic etiology in two fixed-dose studies (total n=179) and two titration studies (total n=149) showed 84% of VIAGRA patients reported improvement in erections compared with 26% of placebo. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA**.** Diary data in two of the studies (n=178) showed rates of successful intercourse per attempt of 70% for VIAGRA and 29% for placebo.
A review of population subgroups demonstrated efficacy regardless of baseline severity, etiology, race and age. VIAGRA was effective in a broad range of ED patients, including those with a history of coronary artery disease, hypertension, other cardiac disease, peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass graft (CABG), radical prostatectomy, transurethral resection of the prostate (TURP) and spinal cord injury, and in patients taking antidepressants/antipsychotics and antihypertensives/ diuretics.
Analysis of the safety database showed no apparent difference in the side effect profile in patients taking VIAGRA with and without antihypertensive medication. This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.

INDICATION AND USAGE
VIAGRA is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS
Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/ or intermittently, in any form is therefore contraindicated.
After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**). In the following patients: age >65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.
VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.

WARNINGS
There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.
VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg), (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**). While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider

whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.
Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including VIAGRA – those with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.
There is no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.
The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (**11-fold increase in AUC**). If VIAGRA is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200–800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended (see **Drug Interactions, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.
Before prescribing VIAGRA, it is important to note the following:
Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including VIAGRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see Drug Interactions) leading to symptomatic hypotension (e.g. dizziness, lightheadedness, fainting).
Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose.
- In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Viagra has systemic vasodilatory properties and may augment the blood pressure lowering effect of other anti-hypertensive medications.
Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted (see **Drug Interactions**).
The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration.
VIAGRA should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).
The safety and efficacy of combinations of VIAGRA with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

In humans, VIAGRA has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and VIAGRA had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

Information for Patients

Physicians should discuss with patients the contraindication of VIAGRA with regular and/or intermittent use of organic nitrates.

Physicians should advise patients of the potential for VIAGRA to augment the blood pressure lowering effect of alpha-blockers and anti-hypertensive medications. Concomitant administration of VIAGRA and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, when VIAGRA is co-administered with alpha-blockers, patients should be stable on alpha-blocker therapy prior to initiating VIAGRA treatment and VIAGRA should be initiated at the lowest dose.

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see **POST-MARKETING EXPERIENCE/Special Senses**).

Physicians should advise patients to stop taking PDE5 inhibitors, including VIAGRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see **ADVERSE REACTIONS, CLINICAL TRIALS and POST-MARKETING EXPERIENCE**).

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Physicians should inform patients not to take VIAGRA with other PDE5 inhibitors including REVATIO. Sildenafil is also marketed as REVATIO for the treatment of pulmonary arterial hypertension. The safety and efficacy of VIAGRA with other PDE5 inhibitors, including REVATIO, have not been studied.

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

Drug Interactions

Effects of Other Drugs on VIAGRA

In vitro studies

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies

Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with VIAGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, in a study performed in healthy male volunteers, coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with VIAGRA (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. VIAGRA had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with VIAGRA (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still approximately 200 ng/mL,

compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see **DOSAGE AND ADMINISTRATION**).

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.) with endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max}. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of VIAGRA on Other Drugs

In vitro studies
Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

In vivo studies
Three double-blind, placebo-controlled, randomized, two-way crossover studies were conducted to assess the interaction of VIAGRA with doxazosin, an alpha-adrenergic blocking agent.

In the first study, a single oral dose of VIAGRA 100 mg or matching placebo was administered in a 2-period crossover design to 4 generally healthy males with benign prostatic hyperplasia (BPH). Following at least 14 consecutive daily doses of doxazosin, VIAGRA 100 mg or matching placebo was administered simultaneously with doxazosin. Following a review of the data from these first 4 subjects (details provided below), the VIAGRA dose was reduced to 25 mg. Thereafter, 17 subjects were treated with VIAGRA 25 mg or matching placebo in combination with doxazosin 4 mg (15 subjects) or doxazosin 8mg (2 subjects). The mean subject age was 66.5 years.

For the 17 subjects who received VIAGRA 25 mg and matching placebo, the placebo-subtracted mean maximum decreases from baseline (95% CI) in systolic blood pressure were as follows:

Placebo-subtracted mean maximum decrease in systolic blood pressure (mm Hg)	**VIAGRA 25 mg**
Supine	7.4 (-0.9, 15.7)
Standing	6.0 (-0.8, 12.8)

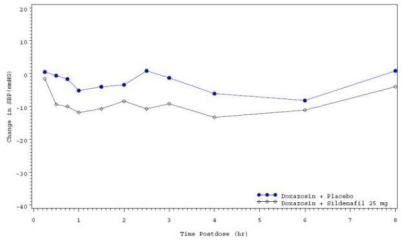


Figure 5: Mean Standing Systolic Blood Pressure Change from Baseline

Blood pressure was measured immediately pre-dose and at 15, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours after VIAGRA or matching placebo. Outliers were defined as subjects with a standing systolic blood pressure of <85 mmHg or a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more timepoints. There were no subjects treated with VIAGRA 25 mg who had a standing SBP < 85mmHg. There were three subjects with a decrease from baseline in standing systolic BP >30mmHg following

VIAGRA 25 mg, one subject with a decrease from baseline in standing systolic BP > 30 mmHg following placebo and two subjects with a decrease from baseline in standing systolic BP > 30 mmHg following both VIAGRA and placebo. No severe adverse events potentially related to blood pressure effects were reported in this group.

Of the four subjects who received VIAGRA 100 mg in the first part of this study, a severe adverse event related to blood pressure effect was reported in one patient (postural hypotension that began 35 minutes after dosing with VIAGRA with symptoms lasting for 8 hours), and mild adverse events potentially related to blood pressure effects were reported in two others (dizziness, headache and fatigue at 1 hour after dosing; and dizziness, lightheadedness and nausea at 4 hours after dosing). There were no reports of syncope among these patients. For these four subjects, the placebo-subtracted mean maximum decreases from baseline in supine and standing systolic blood pressures were 14.8 mmHg and 21.5 mmHg, respectively. Two of these subjects had a standing SBP < 85mmHg. Both of these subjects were protocol violators, one due to a low baseline standing SBP, and the other due to baseline orthostatic hypotension.

In the second study, a single oral dose of VIAGRA 50 mg or matching placebo was administered in a 2-period crossover design to 20 generally healthy males with BPH. Following at least 14 consecutive days of doxazosin, VIAGRA 50mg or matching placebo was administered simultaneously with doxazosin 4 mg (17 subjects) or with doxazosin 8 mg (3 subjects). The mean subject age in this study was 63.9 years.

Twenty subjects received VIAGRA 50 mg, but only 19 subjects received matching placebo. One patient discontinued the study prematurely due to an adverse event of hypotension following dosing with VIAGRA 50 mg. This patient had been taking minoxidil, a potent vasodilator, during the study.

For the 19 subjects who received both VIAGRA and matching placebo, the placebo-subtracted mean maximum decreases from baseline (95% CI) in systolic blood pressure were as follows:

Placebo-subtracted mean maximum decrease in systolic blood pressure (mm Hg)	**VIAGRA 50 mg (95% CI)**
Supine	9.08 (5.48, 12.68)
Standing	11.62 (7.34, 15.90)

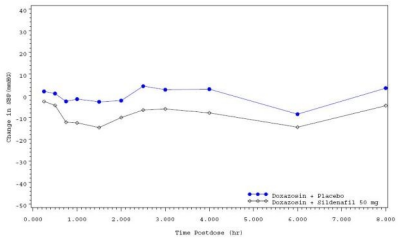


Figure 6: Mean Standing Systolic Blood Pressure Change from Baseline

Blood pressure was measured after administration of VIAGRA at the same times as those specified for the first doxazosin study. There were two subjects who had a standing SBP of < 85 mmHg. In these two subjects, hypotension was reported as a moderately severe adverse event, beginning at approximately 1 hour after administration of VIAGRA 50 mg and resolving after approximately 7.5 hours. There was one subject with a decrease from baseline in standing systolic BP >30mmHg following VIAGRA 50 mg and one subject with a decrease from baseline in standing systolic BP > 30 mmHg following both VIAGRA 50 mg and placebo. There were no severe adverse events potentially related to blood pressure and no episodes of syncope reported in this study.

In the third study, a single oral dose of VIAGRA 100 mg or matching placebo was administered in a 3-period crossover design to 20 generally healthy males with BPH. In dose period 1, subjects were administered open-label doxazosin and a single dose of VIAGRA 50 mg simultaneously, after at least 14 consecutive days of doxazosin. If a subject did not successfully complete this first dosing period, he was discontinued from the study. Subjects who had successfully completed the previous doxazosin interaction study (using VIAGRA 50 mg), including no significant hemodynamic adverse events, were allowed to skip dose period 1. Treatment with doxazosin continued for at least 7 days after dose period 1. Thereafter, VIAGRA 100mg or matching placebo was administered simultaneously with doxazosin 4 mg (14 subjects) or doxazosin 8 mg (6 subjects) in standard crossover fashion. The mean subject age in this study was 66.4 years.

Twenty-five subjects were screened. Two were discontinued after study period 1: one failed to meet pre-dose screening qualifications and the other experienced symptomatic hypotension as a moderately severe adverse event 30 minutes after dosing with open-label

VIAGRA 50 mg. Of the twenty subjects who were ultimately assigned to treatment, a total of 13 subjects successfully completed dose period 1, and seven had successfully completed the previous doxazosin study (using VIAGRA 50 mg).

For the 20 subjects who received VIAGRA 100 mg and matching placebo, the placebo-subtracted mean maximum decreases from baseline (95% CI) in systolic blood pressure were as follows:

Placebo-subtracted mean maximum decrease in systolic blood pressure (mm Hg)	**VIAGRA 100 mg**
Supine	7.9 (4.6, 11.1)
Standing	4.3 (-1.8,10.3)

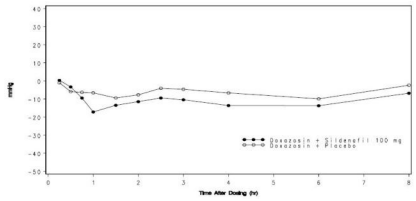


Figure 7: Mean Standing Systolic Blood Pressure Change from Baseline

Blood pressure was measured after administration of VIAGRA at the same times as those specified for the previous doxazosin studies. There were three subjects who had a standing SBP of < 85 mmHg. All three were taking VIAGRA 100 mg, and all three reported mild adverse events at the time of reductions in standing SBP, including vasodilation and lightheadedness. There were four subjects with a decrease from baseline in standing systolic BP >30mmHg following VIAGRA 100 mg, one subject with a decrease from baseline in standing systolic BP > 30 mmHg following placebo and one subject with a decrease from baseline in standing systolic BP > 30 mmHg following both VIAGRA and placebo. While there were no severe adverse events potentially related to blood pressure reported in this study, one subject reported moderate vasodilatation after both VIAGRA 50 mg and 100 mg. There were no episodes of syncope reported in this study.

When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Sildenafil at steady state (80 mg t.i.d.) resulted in a 50% increase in AUC and a 42% increase in C_{max} of bosentan (125 mg b.i.d.).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18–21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use

VIAGRA is not indicated for use in newborns, children, or women.

Pregnancy Category B
No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Geriatric Use
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations**). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

CLINICAL TRIALS
VIAGRA was administered to over 3700 patients (aged 19–87 years) during pre-marketing clinical trials worldwide. Over 550 patients were treated for longer than one year.
In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.
In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.
When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:
TABLE 2. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	**Percentage of Patients Reporting Event**	
	VIAGRA N=734	**PLACEBO N=725**
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*****Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.
In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.
The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:
Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.
Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.
Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.
Hemic and Lymphatic: anemia and leukopenia.
Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.
Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.
Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.
Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.
Special Senses: sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.
Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

POST-MARKETING EXPERIENCE

Cardiovascular and cerebrovascular
Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see **WARNINGS** for further important cardiovascular information).

Special senses
Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including VIAGRA. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of VIAGRA, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors (see **PRECAUTIONS, Information for Patients**).

Other events
Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the clinical trial adverse reactions section above include:

Nervous: seizure, seizure recurrence, anxiety, and transient global amnesia.

Urogenital: prolonged erection, priapism (see **WARNINGS**), and hematuria.

Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see **PRECAUTIONS/Information for Patients**).

OVERDOSAGE
In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were increased.
In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

DOSAGE AND ADMINISTRATION
For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.
The following factors are associated with increased plasma levels of sildenafil: age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome

P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.
Ritonavir greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers (11-fold increase in AUC, see **Drug Interactions**.) Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of VIAGRA in a 48 hour period.
VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.
When VIAGRA is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating VIAGRA treatment and VIAGRA should be initiated at the lowest dose (see **Drug Interactions**).

HOW SUPPLIED
VIAGRA (sildenafil citrate) is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

	25 mg	**50 mg**	**100 mg**
Obverse	VGR25	VGR50	VGR100
Reverse	PFIZER	PFIZER	PFIZER
Bottle of 30	NDC-0069-4200-30	NDC-0069-4210-30	NDC-0069-4220-30
Bottle of 100	N/A	NDC-0069-4210-66	NDC-0069-4220-66

Recommended Storage
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Rx only

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0221-11.0
January 2010

PATIENT SUMMARY OF INFORMATION ABOUT

VIAGRA®
(sildenafil citrate) tablets

This summary contains important information about VIAGRA®. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start taking VIAGRA. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about VIAGRA.
This medicine can help many men when it is used as prescribed by their doctors. However, VIAGRA is not for everyone. It is intended for use only by men who have a condition called erectile dysfunction. **VIAGRA must never be used by men who are taking medicines that contain nitrates of any kind, at any time. This includes nitroglycerin. If you take VIAGRA with any nitrate medicine your blood pressure could suddenly drop to an unsafe or life threatening level.**

• WHAT IS VIAGRA?
VIAGRA is a pill used to treat erectile dysfunction (impotence) in men. It can help many men who have erectile dysfunction get and keep an erection when they become sexually excited (stimulated).
You will not get an erection just by taking this medicine. VIAGRA helps a man with erectile dysfunction get an erection only when he is sexually excited.

• HOW SEX AFFECTS THE BODY
When a man is sexually excited, the penis rapidly fills with more blood than usual. The penis then expands and hardens. This is called an erection. After the man is done having sex, this extra blood flows out of the penis back into the body. The erection goes away. If an erection lasts for a long time (more than 6 hours), it can permanently damage your penis. You should call a doctor immediately if you ever have a prolonged erection that lasts more than 4 hours.
Some conditions and medicines interfere with this natural erection process. The penis cannot fill with enough blood. The man cannot have an erection. This is called erectile dysfunction if it becomes a frequent problem.
During sex, your heart works harder. Therefore sexual activity may not be advisable for people who have heart problems. Before you start any treatment for erectile dysfunction, ask your doctor if your heart is healthy enough to handle the extra strain of having sex. If you have chest pains, dizziness or nausea during sex, stop having sex and immediately tell your doctor you have had this problem.

• HOW VIAGRA WORKS
VIAGRA enables many men with erectile dysfunction to respond to sexual stimulation. When a man is sexually excited, VIAGRA helps the penis fill with enough blood to cause an erection. After sex is over, the erection goes away.

• VIAGRA IS NOT FOR EVERYONE
As noted above (*How Sex Affects the Body*), ask your doctor if your heart is healthy enough for sexual activity.

If you take any medicines that contain nitrates – either regularly or as needed – you should never take VIAGRA. If you take VIAGRA with any nitrate medicine or recreational drug containing nitrates, your blood pressure could suddenly drop to an unsafe level. You could get dizzy, faint, or even have a heart attack or stroke. Nitrates are found in many prescription medicines that are used to treat angina (chest pain due to heart disease) such as:

- nitroglycerin (sprays, ointments, skin patches or pastes, and tablets that are swallowed or dissolved in the mouth)
- isosorbide mononitrate and isosorbide dinitrate (tablets that are swallowed, chewed, or dissolved in the mouth)

Nitrates are also found in recreational drugs such as amyl nitrate or nitrite ("poppers"). If you are not sure if any of your medicines contain nitrates, or if you do not understand what nitrates are, ask your doctor or pharmacist.
VIAGRA is only for patients with erectile dysfunction. VIAGRA is not for newborns, children, or women. Do not let anyone else take your VIAGRA. VIAGRA must be used only under a doctor's supervision.

• WHAT VIAGRA DOES NOT DO

- VIAGRA does not cure erectile dysfunction. It is a treatment for erectile dysfunction.
- VIAGRA does not protect you or your partner from getting sexually transmitted diseases, including HIV—the virus that causes AIDS.
- VIAGRA is not a hormone or an aphrodisiac.

• WHAT TO TELL YOUR DOCTOR BEFORE YOU BEGIN VIAGRA

Only your doctor can decide if VIAGRA is right for you. VIAGRA can cause mild, temporary lowering of your blood pressure. You will need to have a thorough medical exam to diagnose your erectile dysfunction and to find out if you can safely take VIAGRA alone or with your other medicines. Your doctor should determine if your heart is healthy enough to handle the extra strain of having sex.
Be sure to tell your doctor if you:

- have ever had any heart problems (e.g., angina, chest pain, heart failure, irregular heart beats, heart attack or narrowing of the aortic valve)
- have ever had a stroke
- have low or high blood pressure
- have ever had severe vision loss
- have a rare inherited eye disease called retinitis pigmentosa
- have ever had any kidney problems
- have ever had any liver problems
- have ever had any blood problems, including sickle cell anemia or leukemia
- are allergic to sildenafil or any of the other ingredients of VIAGRA tablets
- have a deformed penis, Peyronie's disease, or ever had an erection that lasted more than 4 hours
- have stomach ulcers or any types of bleeding problems
- are taking any other medicines

• VIAGRA AND OTHER MEDICINES

Some medicines can change the way VIAGRA works. Tell your doctor about **any medicines** you are taking. Do not start or stop taking any medicines before checking with your doctor or pharmacist. This includes prescription and nonprescription medicines or remedies:

- Remember, VIAGRA should never be used with medicines that contain nitrates (see *VIAGRA Is Not for Everyone*).
- If you are taking medicines called alpha-blockers for the treatment of high blood pressure or prostate problems, your blood pressure could suddenly drop. You could get dizzy or faint.
- If you are taking a protease inhibitor, your dose may be adjusted (please see *Finding the Right Dose for You*).
- VIAGRA should not be used with any other medical treatments that cause erections. These treatments include pills, medicines that are injected or inserted into the penis, implants or vacuum pumps.

- VIAGRA contains sildenafil, which is the same medicine found in another drug called REVATIO. REVATIO is used to treat a rare disease called pulmonary arterial hypertension. VIAGRA should not be used with REVATIO.

• FINDING THE RIGHT DOSE FOR YOU

VIAGRA comes in different doses (25 mg, 50 mg and 100 mg). If you do not get the results you expect, talk with your doctor. You and your doctor can determine the dose that works best for you.

- Do not take more VIAGRA than your doctor prescribes.

- If you think you need a larger dose of VIAGRA, check with your doctor.

- VIAGRA should not be taken more than once a day.

Your doctor may prescribe a lower dose of VIAGRA in certain circumstances. For example:

- If you are older than age 65, or have serious liver or kidney problems, your doctor may start you at the lowest dose (25 mg) of VIAGRA.

- If you are taking protease inhibitors, such as for the treatment of HIV, your doctor may recommend a 25 mg dose and may limit you to a maximum single dose of 25 mg of VIAGRA in a 48 hour period.

- If you have prostate problems or high blood pressure for which you take medicines called alpha blockers, your doctor may start you on a lower dose of VIAGRA.

• HOW TO TAKE VIAGRA

Take VIAGRA about one hour before you plan to have sex. Beginning in about 30 minutes and for up to 4 hours, VIAGRA can help you get an erection if you are sexually excited. If you take VIAGRA after a high-fat meal (such as a cheeseburger and french fries), the medicine may take a little longer to start working. VIAGRA can help you get an erection when you are sexually excited. You will not get an erection just by taking the pill.

• POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause some side effects. These effects are usually mild to moderate and usually don't last longer than a few hours. Some of these side effects are more likely to occur with higher doses. The most common side effects of VIAGRA are headache, flushing of the face, and upset stomach. Less common side effects that may occur are temporary changes in color vision (such as trouble telling the difference between blue and green objects or having a blue color tinge to them), eyes being more sensitive to light, or blurred vision.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including VIAGRA) reported a sudden decrease or loss of vision in one or both eyes. It is not possible to determine whether these events are related directly to these medicines, to other factors such as high blood pressure or diabetes, or to a combination of these. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including VIAGRA, and call a doctor right away.

In rare instances, men have reported an erection that lasts many hours. You should call a doctor immediately if you ever have an erection that lasts more than 4 hours. If not treated right away, permanent damage to your penis could occur (see *How Sex Affects the Body*).

Sudden loss or decrease in hearing, sometimes with ringing in the ears and dizziness, has been rarely reported in people taking PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the PDE5 inhibitors, to other diseases or medications, to other factors, or to a combination of factors. If you experience these symptoms, stop taking VIAGRA and contact a doctor right away.

Heart attack, stroke, irregular heart beats, and death have been reported rarely in men taking VIAGRA. Most, but not all, of these men had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to VIAGRA.

VIAGRA may cause other side effects besides those listed on this sheet. If you want more information or develop any side effects or symptoms you are concerned about, call your doctor.

• ACCIDENTAL OVERDOSE

In case of accidental overdose, call your doctor right away.

• STORING VIAGRA

Keep VIAGRA out of the reach of children. Keep VIAGRA in its original container. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

• FOR MORE INFORMATION ON VIAGRA

VIAGRA is a prescription medicine used to treat erectile dysfunction. Only your doctor can decide if it is right for you. This sheet is only a summary. If you have any questions or want more information about VIAGRA, talk with your doctor or pharmacist, visit www.viagra.com, or call 1-888-4VIAGRA.

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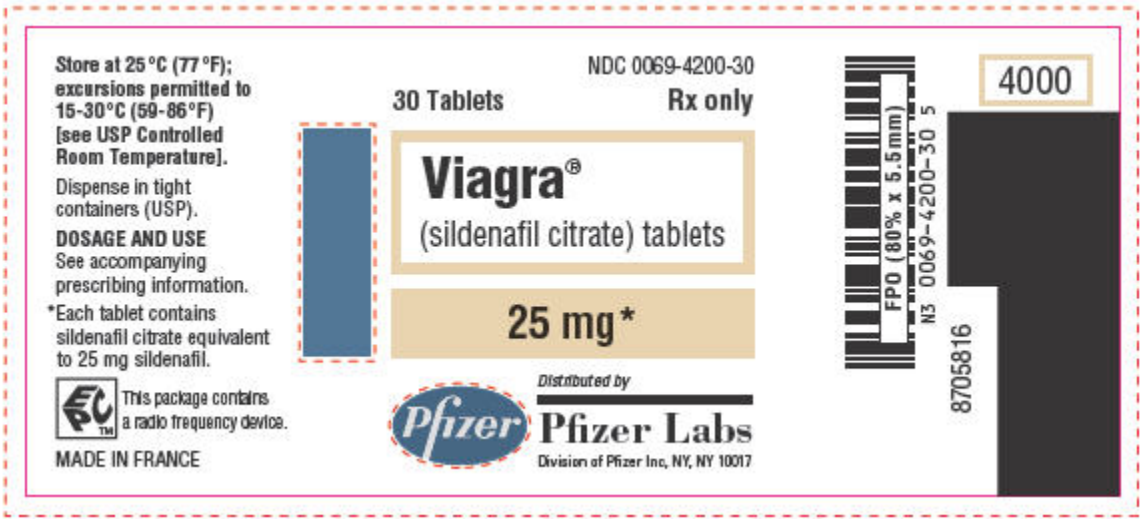
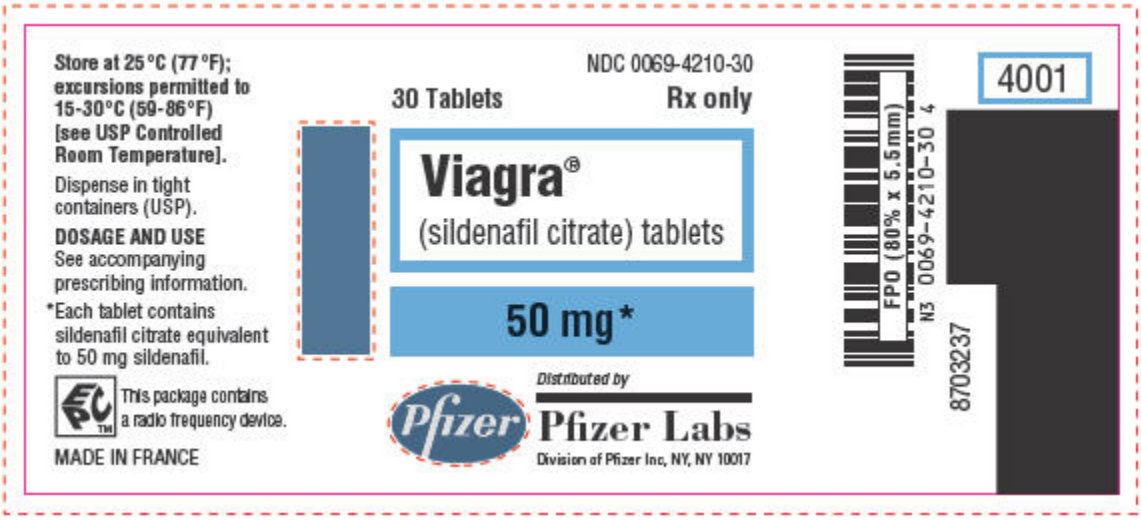
January 2010

PRINCIPAL DISPLAY PANEL - 25MG / 30 TABLET BOTTLE LABEL
NDC 0069-4200-30
30 Tablets
Rx only
Viagra®
(sildenafil citrate) tablets
25 mg*
Pfizer
Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

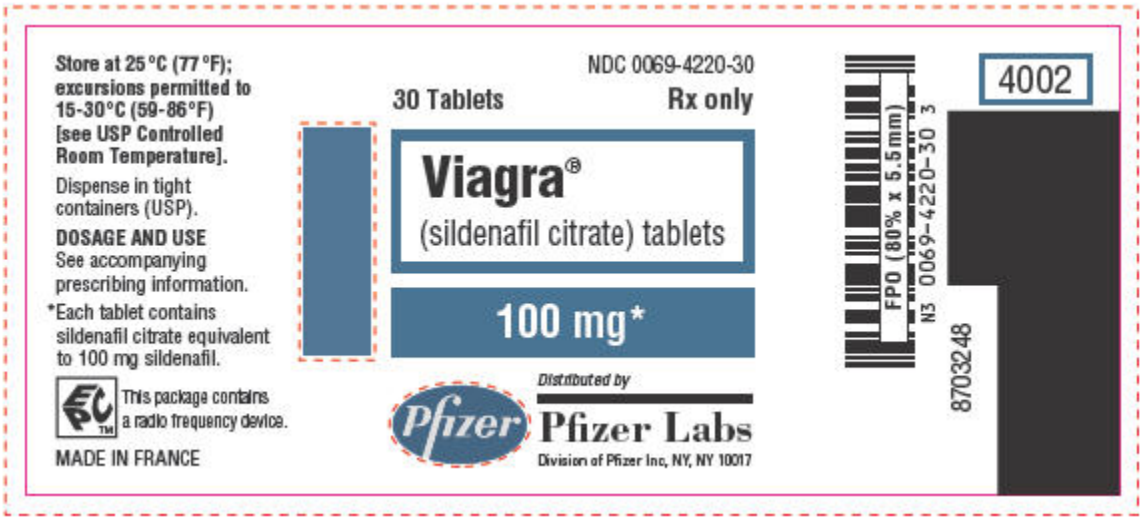


PRINCIPAL DISPLAY PANEL - 50MG / 30 TABLET BOTTLE LABEL
NDC 0069-4210-30
30 Tablets
Rx only
Viagra®
(sildenafil citrate) tablets
50 mg*
Pfizer
Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017



PRINCIPAL DISPLAY PANEL - 100MG / 30 TABLET BOTTLE LABEL
NDC 0069-4220-30

30 Tablets
Rx only
Viagra®
(sildenafil citrate) tablets
100 mg*
Pfizer
Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017



Revised: 07/2009

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